



Brain Metastases

Clinical Case Conference

Palliative Radiotherapy Month

Case

- 70yo M w/ stage IV NSCLC diagnosed in 6/2010 (PET+ pleural plaques, brain MRI negative)
- Initially treated with carboplatin, pemetrexed and avastin, then enrolled on Lucanix ® trial
- Saw med onc 5/31/11 with new onset headache → CT head showed 5 enhancing intracranial masses measuring up to 6mm, as well as a 6mm ependymal nodule
- MRI 6/6 → 5 new enhancing sub-cm lesions

Lesion #1



Lesion #2



Lesion #3

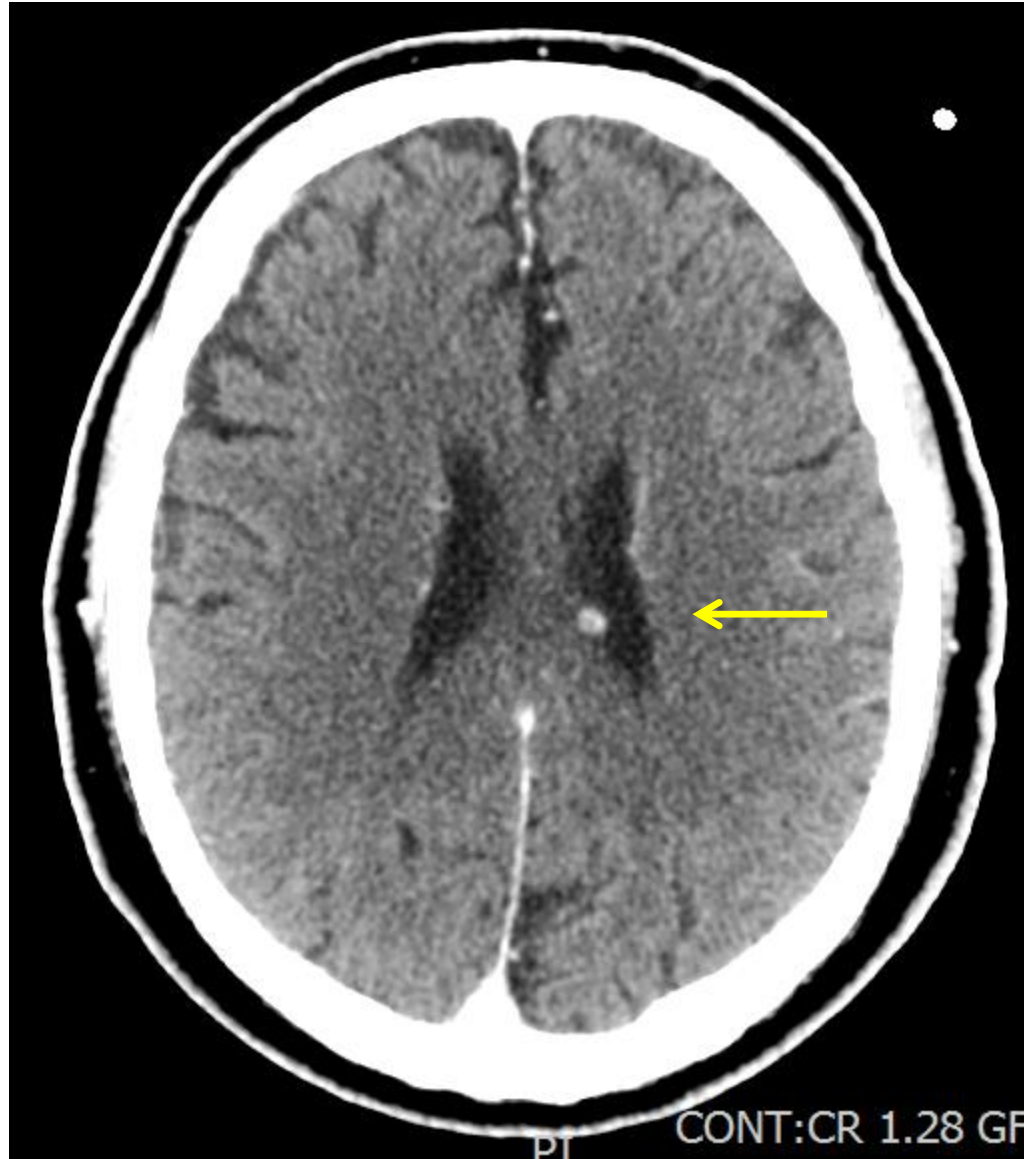


Lesion #4



Lesion #5





6mm ependymal nodule concerning for leptomeningeal involvement

Epidemiology

Primary Site

Lung	50%
Breast	15%–20%
Other known primary	10%–15%
Unknown primary	10%–15%
Melanoma	10%
Colon	5%

Relevant Facts

Median survival	<1 yr
Mean age	60 yr
Annual U.S. incidence	>170,000
Autopsy incidence	10%–30%
Clinical incidence	15%–30%
Metastatic/primary ratio	10:1

Clinical Presentation

H&P:

<i>Symptom</i>	<i>Percentage of Patients</i>	<i>Sign</i>	<i>Percentage of Patients</i>
Headache	49	Hemiparesis	59
Mental problems	32	Cognitive deficits	58
Focal weakness	30	Sensory deficits	21
Ataxia	21	Papilledema	20
Seizures	18	Ataxia	19
Speech problems	12	Apraxia	18

Work-up:

- CT head often ordered initially
- MRI with and without contrast preferred
- If *solitary* met, obtain biopsy

Initial Treatment: Steroids

- Formulation: **dexamethasone** (IV=PO)
- Dose based on symptoms:
 - Asymptomatic → insufficient evidence!
 - Mild → dex **4-8 mg/day**
 - Moderate/severe → dex **16 mg/day (4mg Q6H)**
- Loading dose of 10mg IV preferred
- Concurrent PPI
- Slow taper >2 weeks

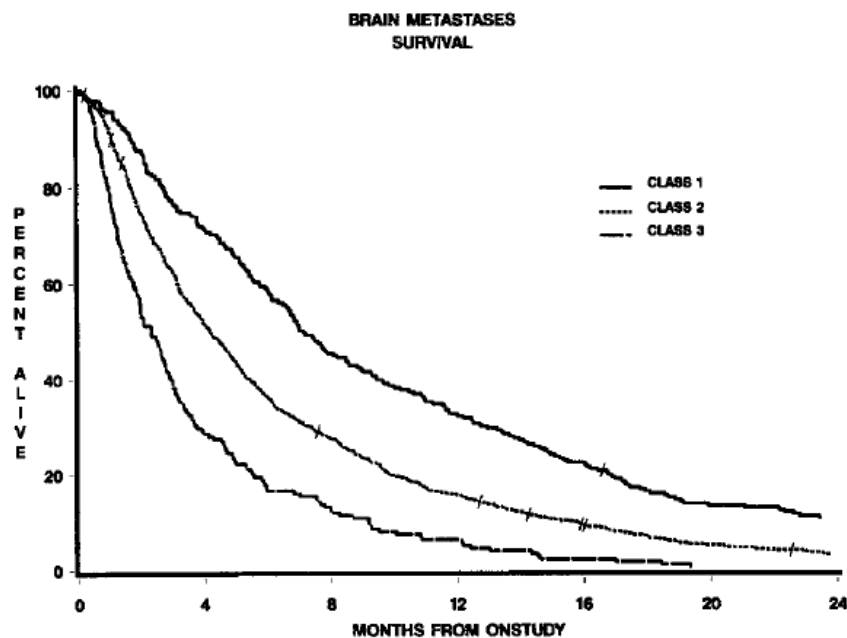
Ryken et al. Journal of Neuro-oncology 2010.

Vecht et al. Neurology 1994.

Prognostic: Recursive Partitioning Analysis (RPA)

RPA Stages For Brain Metastases

Stage	Characteristics	Median Survival (mo)
I	KPS \geq 70, age $<$ 65, primary controlled, no other extracranial mets	7.1
II	all others	4.2
III	KPS $<$ 70	2.3



Prognostic: Graded Prognostic Assessment (GPA)

Table 4. Graded Prognostic Assessment

	Score		
	0	0.5	1.0
Age	>60	50-59	<50
KPS	<70	70-80	90-100
No. of CNS metastases	>3	2-3	1
Extracranial metastases	Present	—	None

GPA range score 0.0-4.0

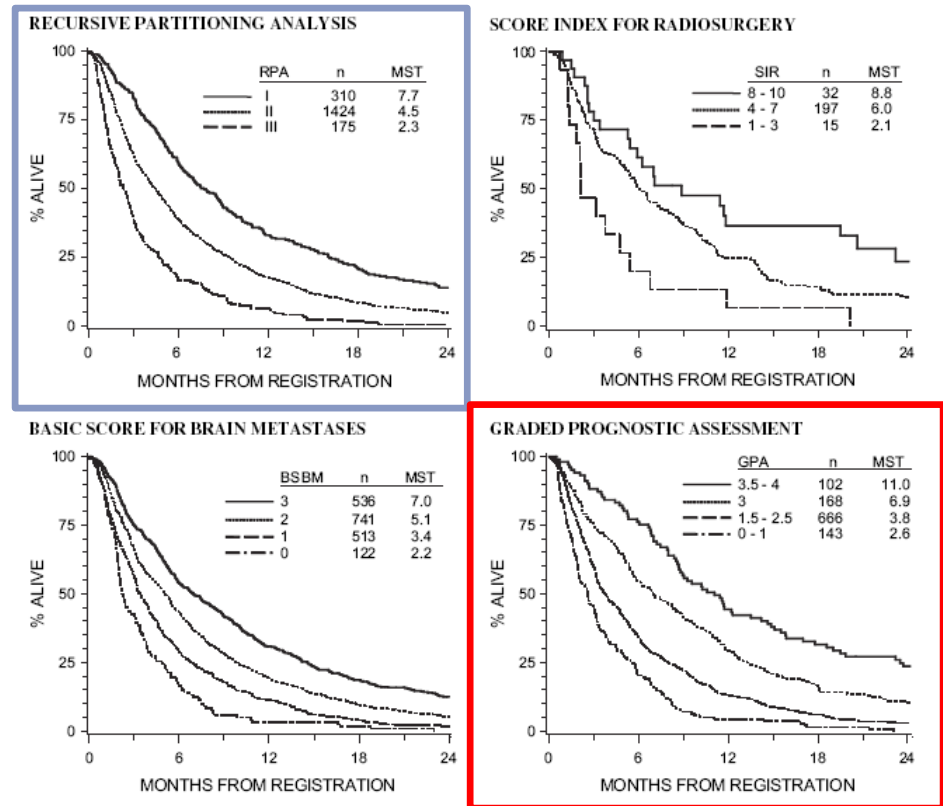


Fig. 1. Kaplan-Meier curves for overall median survival time for each index by individual class and number of patients in each class. SIR = Score Index for Radiosurgery; RPA = recursive partitioning analysis; MST = median survival time.

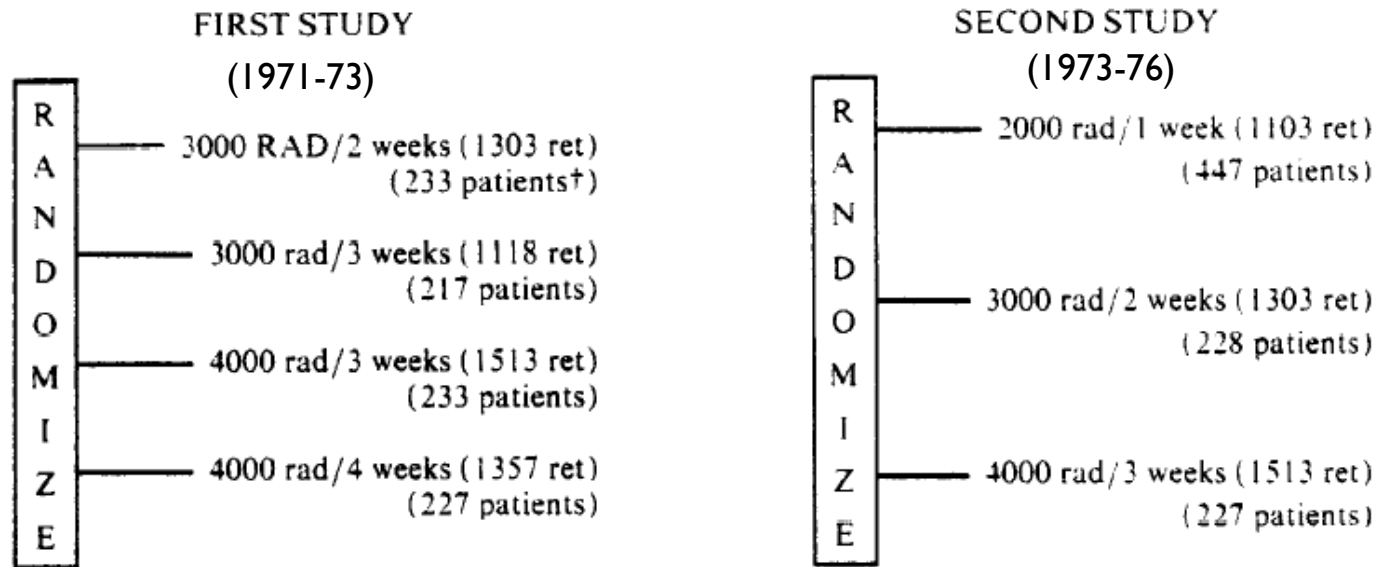
- 4 prognostic groups for GPA, each distinct at $p < .001$
- Highest group (GPA 3.5-4.0) had longest survival of any class in any of the 4 indices (Median Survival Time = 11.0 months)

WBRT Fractionation

TABLE 93.3 SELECTED RANDOMIZED TRIALS EXAMINING VARIOUS FRACTIONATION SCHEDULES FOR BRAIN METASTASIS

<i>Author/Study Group (Reference)</i>	<i>Dose/ Fractions</i>	<i>N</i>	<i>Median Survival</i>	<i>P</i>
Borgelt et al./RTOG (8)	1st study (1971–1973)			
	30 Gy/10	233	21 wk	NS
	30 Gy/15	217	18 wk	
	40 Gy/15	233	18 wk	
	40 Gy/20	227	16 wk	
	2nd study (1973–1976)			
20 Gy/5	447	15 wk	NS	
	30 Gy/10	228	15 wk	
	40 Gy/15	227	18 wk	
Haie-Meder et al./French (10)	25 Gy/10	110	4.2 mo	NS
	(1986–1989)	36 Gy/6 ^a	106	
Priestman et al./Royal College of Radiology (12)	30 Gy/10	263	84 day	.04
	(1990–1993)	12 Gy/2	270	
Murray et al./RTOG-91-04 (11)	30 Gy/10	213	4.5 mo	NS
	(1991–1995)	54.4 Gy/34 ^b	216	
Graham et al./Australia (9)	40 Gy/20 ^c	57	6.1 mo	NS
	(1996–2006)	20 Gy/4	56	

WBRT Fractionation (Borgelt et al)



- RESULT (1980): **No** time-dose response effect seen for neurologic function or palliative index

1981 paper analyzed “ultra-rapid high-dose,” including 4Gyx5

- RESULT: 10Gyx1 and 6Gyx2 were **inferior** in:
 - duration of improvement
 - time to progression of neurologic status, and
 - rate of complete disappearance of neurologic sx

WBRT-related Dementia?

- MSKCC study by DeAngelis et al 1989
 - 232 patients enrolled, only 47 survived to 1 yr
 - Reported 11% risk of **RT-related dementia** at 1 yr
 - 5/47 surviving pts had severe dementia, but... **NONE** treated with 3Gyx10 RT alone
 - Did not utilize sophisticated neurocog testing
 - Later quoted risk closer to 2-5%
- Meyers et al study in JCO 2004
 - 20-60% of pts have impaired cognition at baseline

DeAngelis LM, et al. Neurology 1989.

Meyers CA, et al. J Clin Oncol 2004.

WBRT Overview

- **30 Gy in 10 fractions** is the **standard** for most patients
- Patients treated with *larger fraction sizes* (>3 Gy) or concurrent radiosensitizers are at higher risk for neurologic progression and dementia
- Shorter courses (ie 20Gy in 5 fractions) can be considered for patients with short life expectancy (ie. chemo refractory disease, RPA III)

Single brain met...resect?

TABLE 93.4 RANDOMIZED TRIALS OF SURGICAL RESECTION OF SINGLE BRAIN METASTASIS

Author/Study Group (Reference)	Surgery + RT	RT Alone	P
Patchell et al./University of Kentucky (n = 48) (16)			
Primary end point	(36 Gy/12 fx)		
Overall survival	40 wk	15 wk	<.01
Secondary end points			
Local control			
Local failure	20%	52%	<.02
Time to local failure	>59 wk	21 wk	<.0001
Time to neurologic death	62 wk	26 wk	<.0009
KPS ≥70 maintenance	38 wk	8 wk	<.005
Noordijk et al./Dutch (n = 63) (15)			
Primary end points	(40 Gy/20 fx) ^c		
Overall survival	10 mo	6 mo	.04
FIS ^{1b}	7.5 mo	3.5 mo	.06
Mintz et al./Canadian (n = 84) (14)			
Primary end point	(30 Gy/10 fx)		
Overall survival	5.6 mo	6.3 mo	NS
Secondary end points			
FIS (proportion of days, mean) ^{2b}	32%	32%	NS
Quality of life (Spitzer score)			
1-3 months (mean)	6.38	5.36	NS
4-6 months (mean)	6.32	6.15	NS

Patchell et al. NEJM 1990.

NOTE: 6 of 54 (11%) patients did NOT have brain met at surgery/biopsy:

- 2 abscesses,
- 2 GBMs,
- 2 non-specific inflammatory reactions

RT = whole brain

FIS = functionally independent survival as defined by WHO performance status <2, KPS>70

Surgery +/- WBRT (Patchell 1998)

- Prospective, randomized trial
- Single brain mets, KPS>70%
- 146 eligible pts
 - 46 surgery alone (obs), 49 surgery + WBRT (**50.4Gy/18**)
 - (51 pts refused randomization)
- RESULTS:
 - Brain recurrence lower with RT (18% vs. 70%, $p<0.001$)
 - Time to recurrence longer with RT (>52wks vs. 27wks)
 - RT prevented death due to neuro cause (14% vs. 44%)
 - Overall survival 48wks (RT) vs. 43 wks (obs) (ns)
 - No difference in maintaining KPS>70%

SRS single fraction – safe dose?

- RTOG 90-05 is first SRS clinical trial
- 156 patients with recurrent/previously irradiated brain tumors
- Outcomes: unacceptable toxicities
- RESULTS:
 - Grade 3 = irreversible edema requiring steroids (15 pts)
 - Grade 4 = radionecrosis requiring surgery (15 pts)
 - ~4-5 mon to toxicity

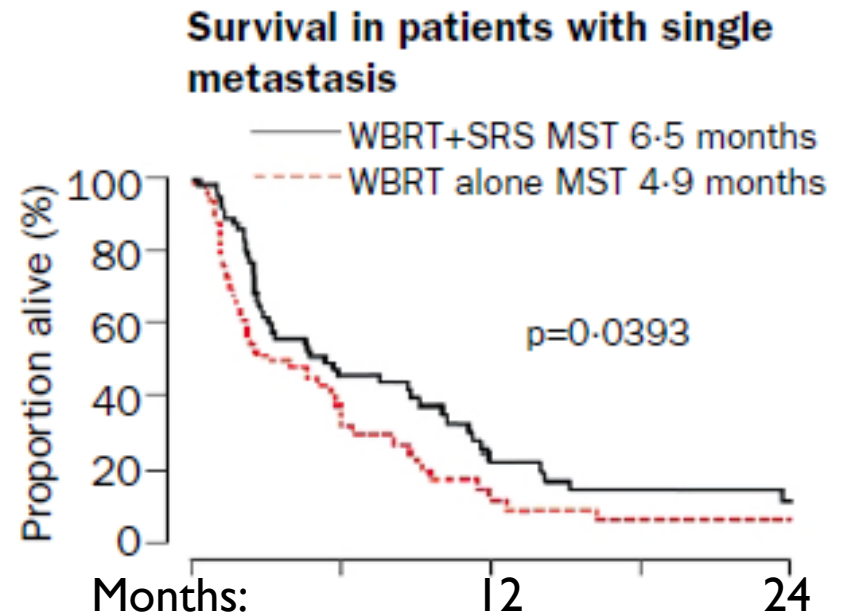
Table 5. Incidence of Grade 3, 4, and 5 CNS toxicity by tumor size and treatment arm

Tumor size*	Arm	Dose	No. of patients	% of Patients With Toxicity		
				Acute	Chronic	Total
≤ 20 mm	1	18 Gy	12	0	8	8
	4	21 Gy	18	0	11	11
	7	24 Gy	10	0	10	10
21–30 mm	2	15 Gy	15	7	7	13
	5	18 Gy	15	0	20	20
	8	21 Gy	13	8	31	38
	11	24 Gy	12	33	25	58
31–40 mm	3	12 Gy	21	5	5	10
	6	15 Gy	22	0	14	14
	9	18 Gy	18	17	33	50

* Maximum tumor diameter.

WBRT +/- SRS (Andrews 2004)

- RTOG 95-08 → randomized, phase III trial
- 333 pts; **1-3 brain mets, <4cm**; RPA 1-2
 - WBRT **37.5Gy/15**
 - WBRT + SRS (24-18-15Gy based on size, per RTOG 90-05)
- Mean OS same (primary endpoint)
- Improved KPS (4% vs 13%) and decreased steroid use at 6 mon but no difference in mental status
- No change in neurologic death
- Subgroup analysis:
 - single met
 - RPA Class I
 - NSCLC or squamous any site



SRS +/- WBRT (Aoyama 2006)

- Randomized, controlled trial
- 132 patients, RPA 1-2
- 1-4 brain mets, each <3cm
- Arms:
 - SRS (22-25Gy up to 2cm, 18-20Gy >2cm)
 - WBRT **30Gy/10** + SRS (reduced 30%)
- RESULTS:

	SRS+WBRT	SRS alone	
Overall survival	7.5 mon	8 mon	ns
Brain tumor recurrence	47%	76%	p<0.001
Functional preservation (KPS>70)	34%	27%	ns
Death due to neuro cause	23%	19.30%	ns

SRS +/- WBRT ... ↓ Neurocog??

- Randomized
- 1-3 mets, RPA 1-2
- SRS vs. SRS + WBRT (30Gy/12)
- Primary endpoint: neurocognitive function (HVLT-R)
- Trial **stopped early** due to decline of total recall in SRS + WBRT arm

	Stereotactic radiosurgery plus whole-brain radiotherapy (N=11)	Stereotactic radiosurgery alone (N=20)	p (A>B)
Total recall	52%	24%	96%
Delayed recall	22%	6%	86%
Delayed recognition	11%	0%	86%

p (A>B)=Bayesian probability that the proportion with a significant neurocognitive worsening is higher in stereotactic radiosurgery plus whole-brain radiotherapy than stereotactic radiosurgery alone.

Table 3: Bayesian posterior mean probability of significant neurocognitive decline at 4 months by treatment group, by Hopkins Verbal Learning Test—Revised

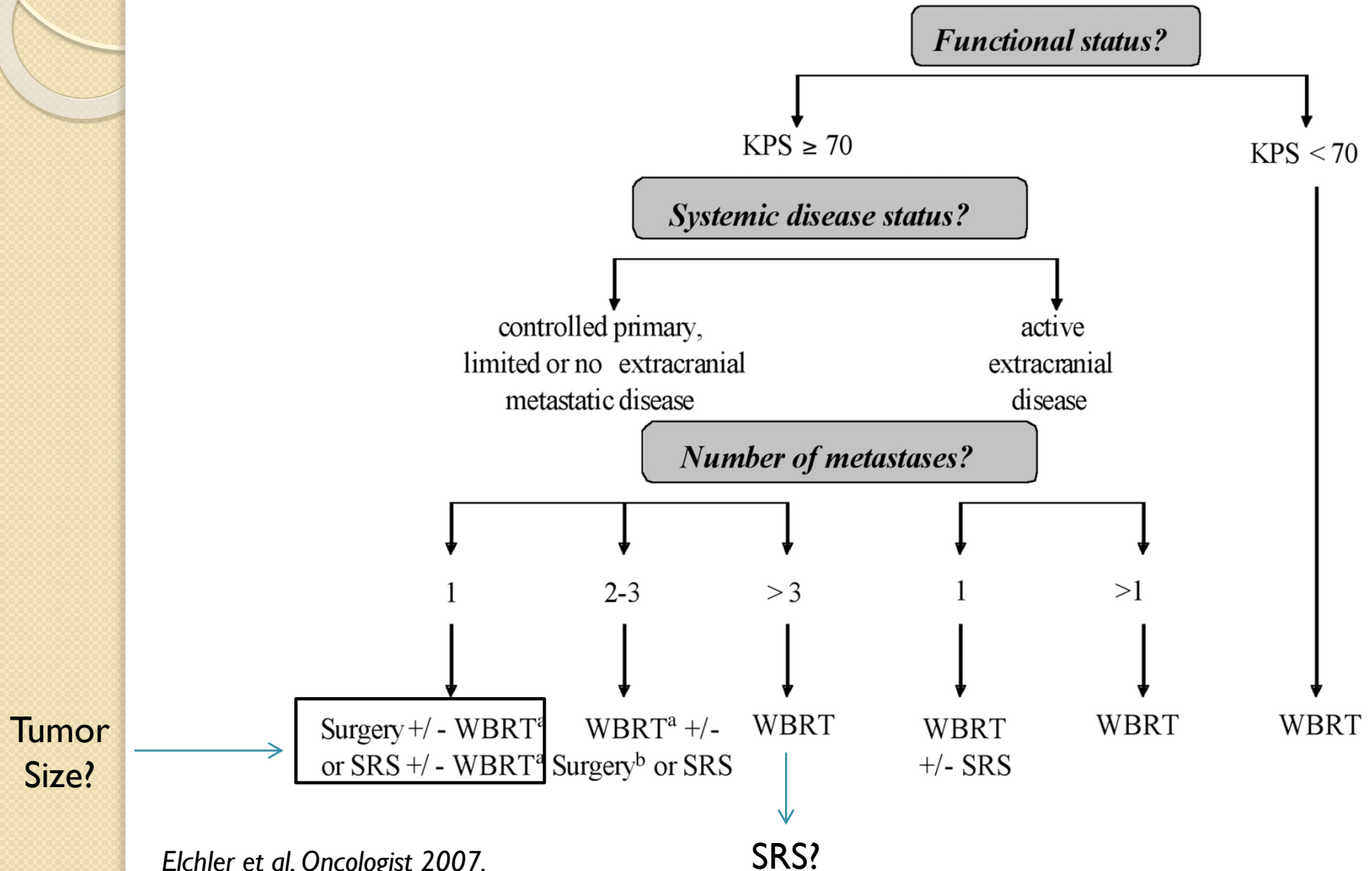
Single brain metastasis (2012 ASTRO guidelines)

- > 3-4 cm, resectable:
 - Surgery +/- WBRT (level 1)
 - Surgery and SRS/radiation boost to cavity (Level 3)
- >3-4cm, NOT resectable
 - WBRT (level 3)
- <3-4cm, resectable
 - Surgery + WBRT (level 1)
 - WBRT + SRS (level 1)
 - SRS alone (level 1)
 - Surgery and SRS/radiation boost to cavity (Level 3)
- <3-4cm, NOT resectable
 - WBRT + SRS (level 1)
 - SRS alone (level 1)

Multiple brain metastasis (2012 ASTRO guidelines)

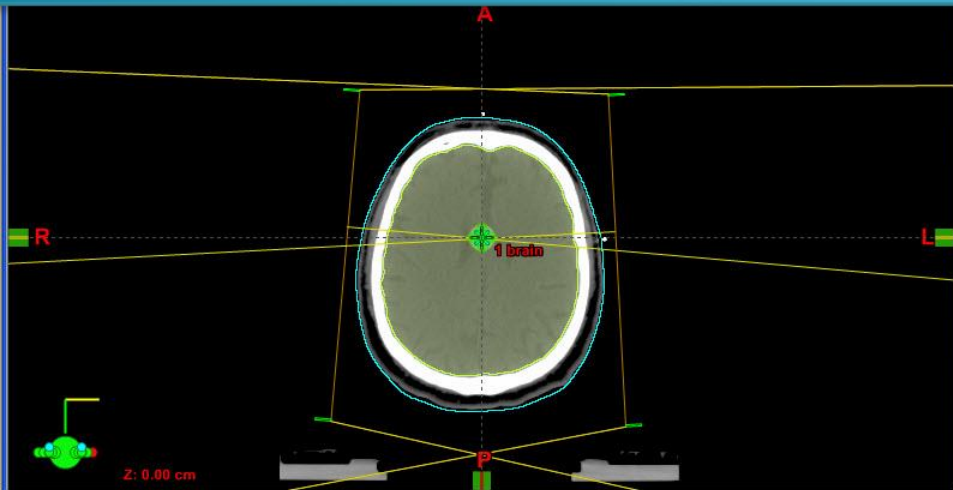
- Each <3-4cm
 - SRS alone (level I)
 - WBRT + SRS (level I)
 - WBRT alone (level I)
 - Consider surgery with post-op WBRT for mass effect (level 3)

Proposed Algorithm

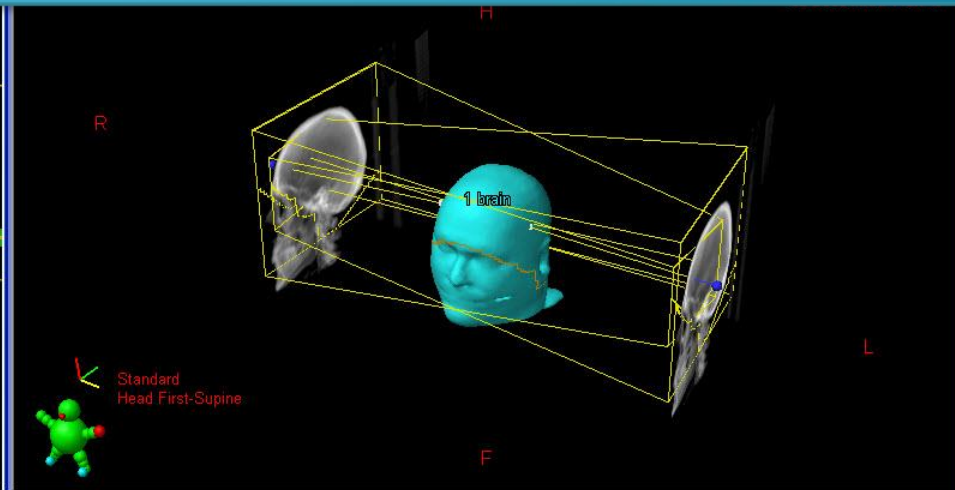


Case

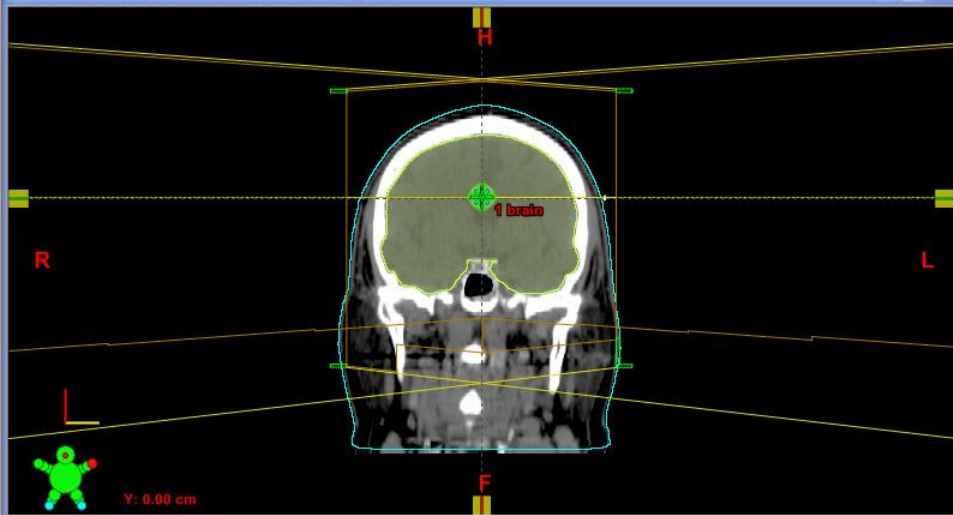
- 70yo M w/ stage IV NSCLC diagnosed on
- 6/2010 PET+ pleural plaques
- 5/31/2011 new onset headache
- 5/31 CT head → 5 enhancing intracranial masses measuring up to 6mm, *concern for leptomeningeal carcinomatosis*
- 6/6 MRI brain → 5 sub-cm nodules
- 6/7 Radiation Oncology consult
- **6/8-21 WBRT (30 Gy in 10 fractions)**



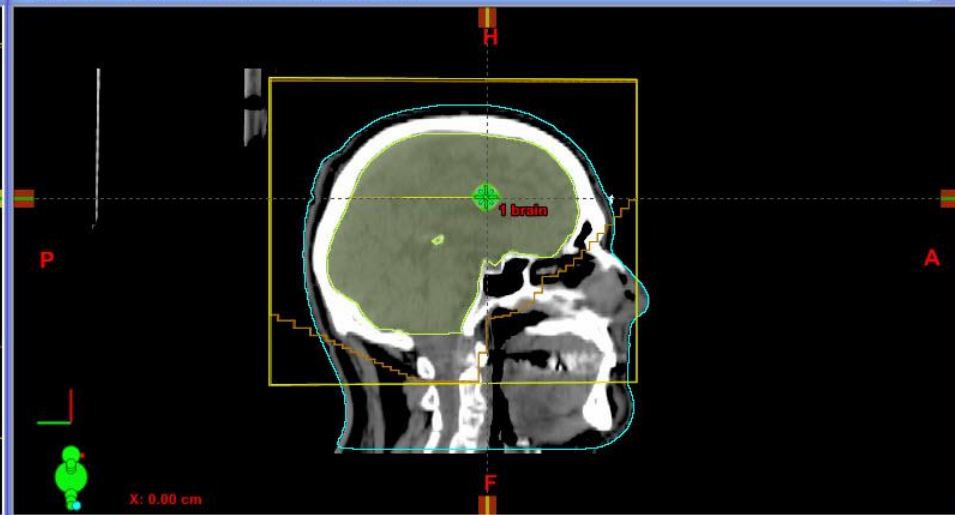
1 brain - Unapproved - Frontal - CT brain 060711



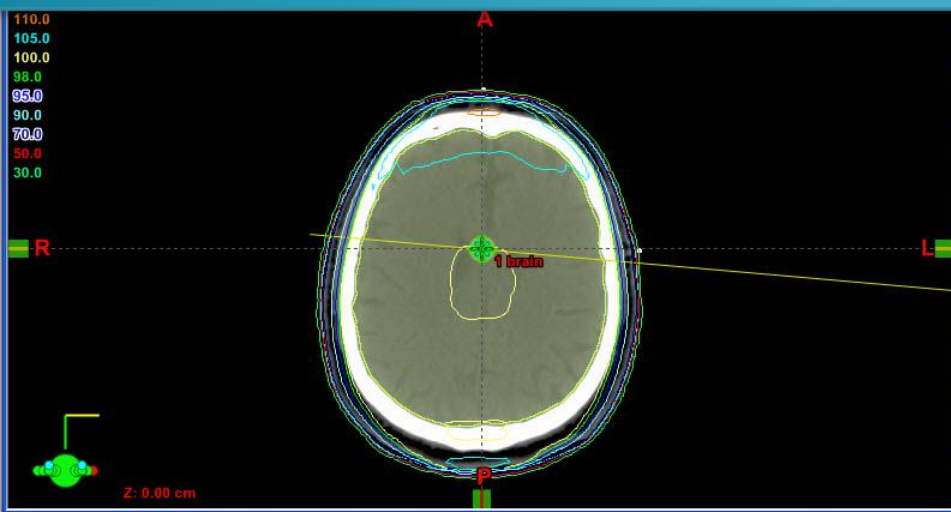
1 brain - Unapproved - Sagittal - CT brain 060711



Selection Registration Contouring Field Setup Plan Evaluation



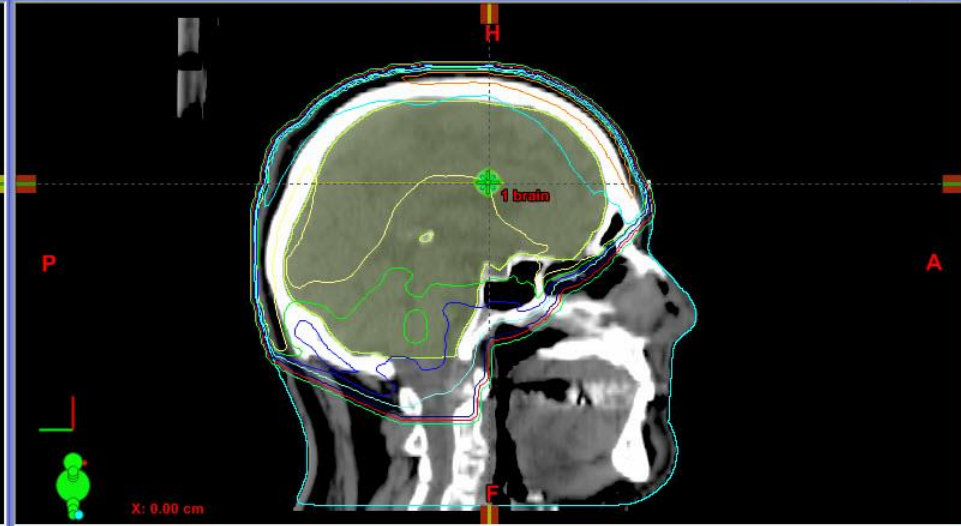
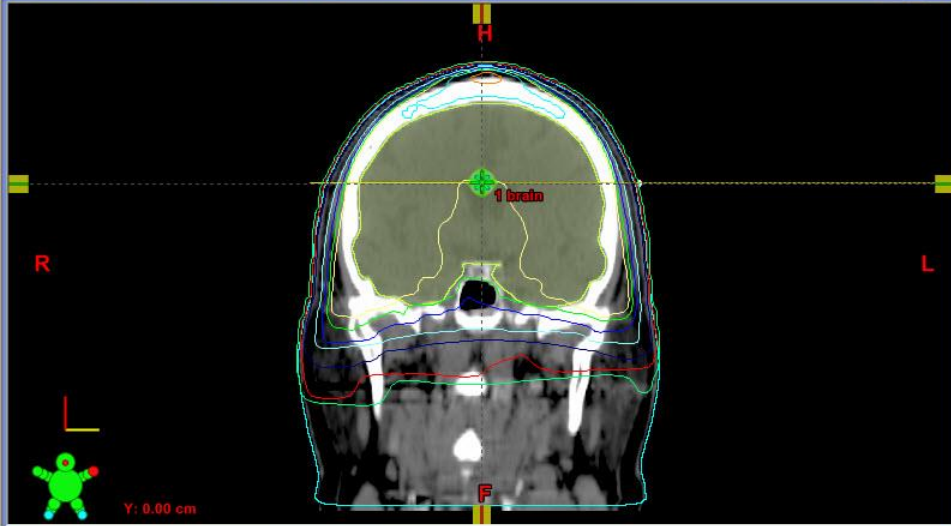
Fields		Dose Prescription		Field Alignments		Plan Objectives		Optimization Objectives		Dose Statistics		Calculation Models		Plan Sum								
Group	Field ID	Technique	Machine/Energy	MLC	Field Weight	Scale	Gantry Rtn [deg]	Coll Rtn [deg]	Couch Rtn [deg]	Wedge	Field X [cm]	X1 [cm]	X2 [cm]	Field Y [cm]	Y1 [cm]	Y2 [cm]	X [cm]	Y [cm]	Z [cm]	SSD [cm]	MU	Ref. D [cGy]
<input checked="" type="checkbox"/>	1 RAO brain	STATIC-I	23EX512 - 6X	Static	1.000	Varian IEC	275.0	90.0	0.0	None	19.2	+11.7	+7.5	23.0	+9.5	+13.5	0.0	0.0	0.0	92.5	170	200.9
<input checked="" type="checkbox"/>	2 LAO brain	STATIC-I	23EX512 - 6X	Static	1.000	Varian IEC	87.0	90.0	0.0	None	19.2	+11.7	+7.5	23.0	+13.5	+9.5	0.0	0.0	0.0	92.6	169	199.4



1 brain - Unapproved - Frontal - CT brain 060711



1 brain - Unapproved - Sagittal - CT brain 060711



Selection Registration Contouring Field Setup Plan Evaluation

Fractionation Id	Dose / Fraction [cGy]	Number of Fractions	Total Dose [cGy]	Primary Reference Point	Total Dose at Primary [cGy]	Relative Dose at Primary [%]	Prescribed Percentage [%]	Plan Normalization Mode	Plan Normalization Value [%]
Fractionation	300.0	10	3000.0	1 brain	3000.0	100.0	100.0	100% in Reference Point 1 brain	200.0

Case

- 70yo M w/ stage IV NSCLC dx 6/2010
- **4/5/2011 ECOG 0**
- 5/31 new HA, CT head → brain mets
- 6/8-21 WBRT (30 Gy in 10 fractions)

- Summer → able to attend son's wedding in Las Vegas
- *11/2 patient passed away on hospice*

- 5 mon survival from dx brain mets
 - RPA Class 2 predicts 4.2 mon
 - GPA score 1.0 predicts 2.6 mon

Thank you!



QUESTIONS?